REMARKS

Preliminary Remarks

Claims 20, 29, 38-40, 62, 75-80, 85-92, 95, 96, 99, and 100 are amended, claims 55, 68 and 81 are canceled, and new claim 101 is added.

Independent claims 20, 29, 80 and 85 are amended to specify that the heavy chain polypeptides of the antibody dimer of the invention comprise a human gamma-1 constant region wherein the C_H2 domain is deleted and the C_H3 domain is fused directly to the hinge region, as described, for example, in Example 2. This amendment incorporates the subject matter of dependent claims 55, 68 and 81, which are canceled.

Claims 38-40, 75-79, 86-92, 95, 96, 99, and 100 are amended to clearly specify that the dimeric antibodies to which the claims are directed are substantially purified. As discussed in the previous response, clear support for the amendment to characterize the disclosed dimeric antibodies as being substantially purified is found in the specification. For example, page 51, lines 23-30 describes the isolation of a mixture of CH2 domain-deleted CC49 antibodies by Protein G affinity chromatography that contains approximately equal amounts (wt/wt) of monomeric (H_2L_2) and dimeric (H_4L_4) CH2 domain-deleted CC49 antibodies (*see* Figure 9). Such a preparation in which a significant weight fraction of the antibodies present are monomeric (H_2L_2) CH2 domain-deleted antibodies is not considered by the applicant, and would not reasonably be considered by one of skill in the art, to be a preparation of substantially purified dimeric (H_4L_4) CH2 domain-deleted antibodies. On the other hand, page 52, lines 1-14, describes further treating the mixture of monomeric (H_2L_2) and dimeric (H_4L_4) antibodies described on page 51 to separate the monomeric (H_2L_2) antibodies from the dimeric (H_4L_4) antibodies (by size-exclusion chromatography), to produce a preparation of dimeric (H_4L_4) CH2 domain-deleted antibodies of greater than 98% homogeneity. Such a preparation that is largely free of contaminants, including monomeric (H_2L_2) CH2 domain-deleted antibodies, is considered by the applicants, and would likewise be regarded by persons of skill in the art, as a preparation of substantially purified dimeric (H_4L_4) CH2 domain-deleted antibodies.

New claim 101 is directed to purified dimeric antibodies that bind specifically to TAG-72, wherein each dimeric antibody comprises two antibodies that are non-covalently associated to form a tetravalent antibody dimer having four antigen-binding sites that bind specifically to TAG-72, and

each of the antibodies in the dimer comprises two antibody heavy chain polypeptides having the heavy chain variable region amino acid sequence shown in Figure 4A (SEQ ID NO: 7), and two antibody light chain polypeptides having the light chain variable region amino acid sequence shown in Figure 5A (SEQ ID NO: 9), and has two antigen-binding sites that bind specifically to TAG-72; wherein each of the four antibody heavy chain polypeptides in the dimeric antibody comprises a human gamma-1 constant region wherein a C_H2 domain is deleted from, and a C_H3 domain is fused directly to the hinge region; and wherein the dimeric antibodies are substantially purified to homogeneity. Support for new claim 101 is found in the specification, *e.g.*, on page 52.

Patentability Remarks

35 U.S.C. §103(a)

Claims 20, 29, 38-40, 62-63, 75-80, and 84-100 are rejected under 35 U.S.C. §103(a) as allegedly being obvious in view of Gillies et al. (1990, Human Antibodies and Hybridomas, 1(1):47-54), as evidenced by the specification, in view of Kashmiri et al. (5/11/2000, WO 00/26394), Anderson et al. (U.S. Patent No. 6,348,581 B1) and Thorpe et al. (U.S. Patent No. 6,342,219 B1).

In the response to the final official action that was filed on July 6, 2006, independent claims 20, 29, 80, and 85 were amended to be directed to dimeric, tetravalent (H_4L_4) CH2 domain-deleted anti-TAG72 antibodies, or to a kit containing such antibodies, which dimeric, tetravalent (H_4L_4) CH2 domain-deleted anti-TAG72 antibodies are substantially purified.

In the advisory action dated July 19, 2006, the examiner maintained the rejection of the claims under 35 U.S.C. §103(a) as being obvious in view of Gillies et al., as evidenced by the specification, in view of Kashmiri et al., Anderson et al., and Thorpe et al. In support of maintaining the rejection, the examiner repeated the argument in the final official action that dimeric, tetravalent (H_4L_4) CH2 domain-deleted anti-TAG72 antibodies of the claimed invention would form spontaneously in a composition of chimeric CH2 domain-deleted anti-TAG72 antibodies prepared according to the teachings of Gillies et al., in view of Kashmiri et al., Anderson et al., and Thorpe et al., and that "when claimed and prior art products are produced by identical or substantially identical processes, a prima facie case of obviousness has been

established," *citing In re* Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA1977). *See* page 5, lines 14-16, of the final official action dated March 3, 2006, and page 2, lines 19-20, of the advisory action. With regard to the added limitation in the claims that the dimeric, tetravalent, CH2 domain-deleted anti-TAG72 antibodies of the claimed invention are substantially purified, the examiner alleges that it would have been obvious to prepare the substantially purified dimeric, tetravalent, CH2 domain-deleted anti-TAG-72 antibodies of the claimed invention, "in view of the well-known and standard purification techniques in the art that are similar to the disclosed methods for purifying the humanized CC49 CH2 domain-deleted antibodies." In support of this argument, the examiner cites Kashmiri et al. (page 17, lines 20-24) as teaching that the disclosed anti-TAG-72 CC49 antibodies "can be purified according to standard procedures of the art, including ammonium sulfate precipitation, affinity columns, column chromatography, and gel electrophoresis," to from about 90% to 99% or more homogeneity, and cites Thorpe et al. (col. 61, lines 10-19) as teaching antibody techniques such as protein G and HPLC columns that are also disclosed in the present application. *See* page 2, lines 30-39, of the advisory action dated July 19, 2006.

For the reasons discussed below, the applicants submit that Gillies et al., either alone or in combination with the secondary references, would have provided one of ordinary skill in the art at the time the invention was made with a suggestion or motivation to modify or combine the teachings of the cited references to prepare the purified dimeric, tetravalent (H_4L_4), CH2 domain-deleted antibodies of the claimed invention. In fact, at the time the invention was made, one of ordinary skill in the art did not know that dimeric (H_4L_4, 240 kDa) CH2 domain-deleted antibodies of the claimed invention even existed, so the cited references, alone or in combination, could not have described or suggested making or using purified dimeric (H_4L_4) CH2 domain-deleted antibodies of the claimed invention. Moreover, as discussed below, at the time the invention was made there was no reasonable expectation that one of ordinary skill in the art would have used known, standard antibody purification methods to successfully purify dimeric, tetravalent (H_4L_4), CH2 domain-deleted antibodies of the claimed invention.

To establish a *prima facie* case of obviousness, the examiner must show that the prior art references themselves or the knowledge generally available to one of

ordinary skill in the art would (1) provide some suggestion or motivation to modify or combine reference teachings to obtain the claimed invention, (2) teach or suggest all of the claim limitations, and (3) provide a reasonable expectation that the claimed invention can be made or used successfully. *In re* Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). *See* M.P.E.P. § 2142.

In determining if there is obviousness in the first instance, "it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re* Linter, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972). Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re* Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re* Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). *See* M.P.E.P. § 2142.

Proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re* Hedges, 783 F.2d 1038, 228 USPQ 686 (Fed. Cir. 1986). *See* M.P.E.P. § 2145(X)(D)(3). It is improper to combine references where the references teach away from their combination. *In re* Graselli, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). *See* M.P.E.P. § 2145(X)(D)(2).

A. No suggestion or motivation to modify or combine the teachings of the cited references to obtain the claimed invention

As pointed out above, the claims are amended to specify that the dimeric, tetravalent (H_4L_4) CH2 domain-deleted anti-TAG72 antibodies of the claimed invention are substantially purified. Prior to the applicant's discovery and purification of dimeric, tetravalent (H_4L_4), CH2 domain-deleted antibodies, it was simply not known that such dimeric antibody complexes existed. **Gillies et al. in combination with the cited secondary references would not have provided one of ordinary skill in the art at the time the invention was made with a**

suggestion or motivation to modify or combine the teachings of the cited references to prepare the purified dimeric, tetravalent (H_4L_4), CH2 domain-deleted antibodies of the claimed invention.

Gillies *et al.* describe a method for preparing chimeric, CH2 domain-deleted anti-TAG-72 antibodies, and teach that their method results in the formation of 60 kDa HL "half-molecules" that contain one light chain and one ΔCH2 heavy chain, and 120 kDa H_2L_2 molecules consisting of two 60 kDa HL "half-molecules." Gillies et al. describe analyzing the CH2 domain-deleted antibody molecules produced by their method with non-denaturing HPLC size exclusion chromatography, and teach that the 60 kDa HL antibodies and the 120 kDa H_2L_2 molecules "migrate as one peak" during non-denaturing size exclusion chromatography. Based on their results obtained using HPLC size exclusion chromatography, Gillies *et al.* conclude that the ΔCH2 HL antibodies produced by their method are present as 120 kDa H_2L_2 molecules (either in disulfide-linked H_2L_2 molecules, or in H_2L_2 molecules held together by non-covalent interactions). *See* page 50, left column. Moreover, although Gillies et al. performed HPLC size exclusion chromatography on the mixture of antibody molecules produced by their method, they do not describe observing the dimeric (H_4L_4, 240 kDa) CH2 domain-deleted anti-TAG-72 antibodies of the claimed invention, or even suggest that such dimeric (H_4L_4, 240 kDa) CH2 domain-deleted antibodies might exist. **Gillies et al. therefore provided no suggestion or motivation to one of ordinary skill in the art at the time the invention was made to prepare CH2 domain-deleted anti-TAG-72 antibodies according to their method, and then to purify from the resulting mixture the purified dimeric (H_4L_4, 240 kDa) CH2 domain-deleted anti-TAG-72 antibodies of the present invention.**

The applicants submit that the secondary references do not overcome the failings of the primary reference. Specifically, the applicants submit that the general teachings of Kashmiri et al. and Thorpe et al. and the generally available knowledge regarding standard methods for purifying antibodies, in combination with the teachings of the Gillies et al. and the cited secondary references regarding preparing CH2 domain-deleted anti-TAG72 antibodies, would not have provided one of ordinary skill in the art at the time the application was filed with a suggestion or motivation to modify or combine the teachings of the cited references to obtain the

substantially purified dimeric, tetravalent (H_4L_4) CH2 domain-deleted anti-TAG72 antibodies of the claimed invention.

The examiner alleges that it would have been obvious to prepare the substantially purified dimeric, tetravalent, CH2 domain-deleted anti-TAG72 antibodies of the claimed invention, in view of the well-known and standard purification techniques in the art that are similar to the disclosed methods for purifying the humanized CC49 CH2 domain-deleted antibodies," as described by Kashmiri et al. and Thorpe et al. *See* page 2, lines 30-39, of the advisory action dated July 19, 2006. The teachings of the secondary references, Kashmiri et al. and Thorpe et al., with regard to purification of the dimeric (H_4L_4, 240 kDa) CH2 domain-deleted anti-TAG-72 antibodies of the present invention, are described above and are generic in form. In particular, Kashmiri et al. teaches using "standard procedures" for antibody purification, "including ammonium sulfate precipitation, affinity columns, column chromatography, and gel electrophoresis" (*see* page 17, lines 20-24); and Thorpe et al. teaches that the antibodies can be purified "using filtration, centrifugation, and various chromatographic methods such as HPLC or affinity chromatography" that are "well known to those of skill in the art." (col. 61, lines 10-19).

The examiner's allegation that purification of the dimeric (H_4L_4, 240 kDa) CH2 domain-deleted anti-TAG-72 antibodies of the present invention would have been obvious is without scientific basis. Most of the methods identified by the cited references as "standard" techniques, *e.g.*, filtration and ammonium sulfate precipitation, and most commonly used forms of standard and high pressure liquid chromatography (HPLC), such as ion exchange, affinity, and reverse phase chromatography, would not be expected to successfully separate dimeric (H_4L_4, 240 kDa) CH2 domain-deleted anti-TAG-72 antibodies of the present invention from the monomeric (H_2L_2, 120 kDa) CH2 domain-deleted anti-TAG-72 antibodies described by Gillies et al. Moreover, Gillies et al. taught that the CH2 domain-deleted, HL and H_2L_2 anti-TAG-72 antibodies produced by their method are co-purified by HPLC size exclusion chromatography as complexes having molecular weight of 120 kDa, and did not report observation of dimeric (H_4L_4, 240 kDa) CH2 domain-deleted anti-TAG-72 antibodies of the present invention, as discussed above. Therefore, even if one of one of ordinary skill in the art did perform HPLC size exclusion chromatography to purify the CH2 domain-deleted, HL and H_2L_2 anti-TAG-72

antibodies as described by Gillies et al., they would reasonably be expected to isolate the antibodies from the fractions corresponding to molecules having molecular weight of 120 kDa. Gillies et al. describe purifying CH2 domain-deleted anti-TAG-72 antibodies to greater than 90% homogeneity by a purification protocol comprising protein A chromatography followed by immunoaffinity chromatography. Neither of these chromatographic methods is expected to separate the CH2 domain-deleted antibody molecules having molecular weight of 120 kDa described by Gillies et al. from dimeric, H_4L_4 CH2 domain-deleted antibodies having molecular weight of 240 kDa of the present invention. There is no suggestion or motivation in the prior art to assay for or purify the dimeric, H_4L_4 CH2 domain-deleted anti-TAG-72 antibodies having molecular weight of 240 kDa of the present invention. Furthermore, there is no suggestion or motivation in the art to select and use size exclusion media that is capable of separating the 120 kDa CH2 domain-deleted antibody molecules described by Gillies et al. from the 240 kDa dimeric, H_4L_4 CH2 domain-deleted anti-TAG-72 antibodies of the present invention. Moreover, in teaching that HPLC size exclusion chromatography fails to separate the species of ΔCH2 antibodies produced by their method, Gillies et al. actually taught away from using HPLC size exclusion chromatography as a method for purifying CH2 domain-deleted anti-TAG-72 antibodies to homogeneity.

In view of the foregoing, and given the teaching of Gillies et al. that CH2 domain-deleted anti-TAG-72 antibodies are purified by non-denaturing HPLC size exclusion chromatography as complexes having molecular weight of 120 kDa, as discussed above, Gillies et al., in combination with the cited secondary references (i.e., Kashmiri et al. and Thorpe et al.), simply would not have provided suggestion or motivation to one of ordinary skill in the art at the time the invention to use known antibody purification methods to prepare the purified dimeric (H_4L_4, 240 kDa) CH2 domain-deleted anti-TAG-72 antibodies of the claimed invention.

B. No description or suggestion to make or use purified dimeric (H_4L_4) CH2 domain-deleted antibodies of the claimed invention.

As pointed out above, to establish a *prima facie* case of obviousness, the examiner must show that the prior art references themselves or the knowledge generally available to one of ordinary skill in the art would teach or suggest all of the claim limitations. At the time the invention was made, the prior art did not teach or suggest, and persons of ordinary skill in the art did not know or suspect, that 240 kDa dimeric, H_4L_4 CH2 domain-deleted anti-TAG-72 antibodies of the claimed invention existed or could be formed. Accordingly, neither the prior art nor the knowledge generally available to one of ordinary skill in the art at the time the invention was made would have taught or suggested making or using the purified dimeric (H_4L_4, 240 kDa) CH2 domain-deleted anti-TAG-72 antibodies of the claimed invention.

C. No reasonable expectation that use of known, standard antibody purification methods would to successfully purify dimeric, tetravalent (H_4L_4), CH2 domain-deleted antibodies of the claimed invention.

Gillies et al. reported what they describe as the "surprising" and "unexpected" finding that the apparent antigen binding activity of the CH2 domain-deleted antibodies produced by their method is significantly higher than that of the corresponding wild-type antibodies (*e.g., see* page 49, right column, and page 53, left column). Gillies et al. describe experiments they performed in an unsuccessful effort to determine the structural basis for the observed increased antigen binding activity of the CH2 domain-deleted antibodies produced by their method (*see* pages 50-52 and page 53, right column). As discussed above, Gillies et al. described using HPLC size exclusion chromatography to analyze the CH2 domain-deleted anti-TAG-72 antibodies produced by their method, but did not describe observing dimeric, H_4L_4 CH2 domain-deleted anti-TAG-72 antibodies having molecular weight of 240 kDa of the present invention, **even though they were actively seeking a structural basis for the high antigen binding affinities that they observed**. The failure of Gillies et al. to observe and purify dimeric, H_4L_4 CH2 domain-deleted anti-TAG-72 antibodies having molecular weight of 240 kDa of the present invention, even when they were actively looking for antibody structures that might explain the high antigen binding affinities they observed, is strong evidence that identification and dimeric, H_4L_4 CH2 domain-deleted anti-TAG-72 antibodies having molecular weight of 240 kDa of the present invention would not have been obvious at the time the invention was made. Without

knowing of the existence of dimeric (H_4L_4, 240 kDa) CH2 domain-deleted anti-TAG-72 antibodies of the present invention, it is likely that one of ordinary skill in the art would have failed to detect and purify the dimeric (H_4L_4, 240 kDa) CH2 domain-deleted antibodies of the claimed invention, just as Gillies et al. failed to do so. Contrary to the examiner's allegations in the advisory action, it would have been impossible to predict that at the time the invention was made, one of ordinary skill in the art using well-known, standard techniques for purifying antibodies would reasonably have been expected to prepare the substantially purified dimeric (H_4L_4, 240 kDa) CH2 domain-deleted anti-TAG-72 antibodies of the present invention.

For the reasons discussed above, the claimed invention therefore would not have been obvious to one of ordinary skill in the art at the time the invention was made in view of Gillies et al. (1990), as evidenced by the specification, and further in view of Kashmiri et al., Anderson et al., and Thorpe et al., and withdrawal of the rejection of claims 20, 29, 38-40, 62-63, 75-80, and 84-100 under 35 U.S.C. § 103(a) is respectfully requested.

Declaration under 37 C.F.R. § 1.132 regarding unexpected properties of the claimed invention

The application discloses experimental results that demonstrate the unpredicted and surprising discovery that the purified dimeric, tetravalent (H_4L_4, 240 kDa), CH2 domain-deleted antibodies of the claimed invention bind to TAG-72 antigen with significantly higher binding activity than the corresponding monomeric (H_2L_2) CH2 domain-deleted anti-TAG-72 antibodies. As described in Example 7, purified monomeric (H_2L_2, 120 kDa) CH2 domain-deleted antibodies bind to TAG-72 antigen with an apparent dissociation constant of 2.3 nM, whereas purified dimeric (H_4L_4) CH2 domain-deleted antibodies of the claimed invention bind to TAG-72 antigen with an apparent dissociation constant of 0.15 nM. The purified dimeric (H_4L_4) CH2 domain-deleted antibodies of the claimed invention are thus shown by the present application to bind to TAG-72 antigen with 15-fold greater binding activity than monomeric (H_2L_2, 120 kDa) CH2 domain-deleted antibodies (data shown in Figure 11A).

The applicant considers the 15-fold increase in antigen binding activity of the dimeric (H_4L_4, 240 kDa) CH2 domain-deleted anti-TAG-72 antibodies of the present invention, over the

antigen binding activity of the corresponding monomeric (H_2L_2, 120 kDa) CH2 domain-deleted antibodies, to be an unexpected and advantageous property of the claimed invention. If a declaration under 37 C.F.R. § 1.132 by a scientist in the field is considered necessary to establish that the disclosed properties of the claimed invention are unexpected and advantageous with respect to CH2 domain-deleted antibodies of the prior art, the examiner is asked to inform the applicant that this is the case, and the applicant will readily provide such a declaration.

CONCLUSION

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If the examiner identifies any points that he feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Please charge any fees or credit any overpayments associated with the submission of this response to Deposit Account Number 03-3975.

Respectfully submitted,

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